The YEAR BOOK of

Dermatology

1975

Edited by

FREDERICK D. MALKINSON, M.D.

and

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YEAR BOOK MEDICAL PUBLISHERS, INC.
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75th Anniversary Edition

Publisher's Foreword

This year marks the 75th anniversary of the publication of the Year Book series, the only books of their type to be published continuously since the turn of the century.

The concept for the Year Books was originated in 1900 by Gustavus P. Head, a Chicago physician, who felt that there was a need for a series of books that would present a digested selection of much of the best medical literature of the year in a volume convenient for reference. He believed that the value of the series to the reader would be enhanced by having outstanding medical editors add brief critical comments to evaluate the articles that they selected.

From 1900 until the end of World War I, most physicians were general practitioners with broad interests. Their information needs were satisfied by subscribing to the 10 original Year Books as a series. After World War I, there was a significant rise in specialization within the medical profession. In 1922, reflecting this trend, advertisements for single Year Books were mailed to specialists for the first time. The response was unprecedented and thousands of orders were received. Today, a Year Book is available to meet the needs of the physician in each major specialty area and in many of the subspecialty areas.

As specialization increased, there was an even greater increase in the complexity of the medical journal literature and in the number of journals published. To adequately cover the greater number of significant articles and to allow for better concentration of material for the physicians in specialty areas, the number of Year Books in the series was gradually increased. By 1940 there were 15 Year Books; the number increased to 16 in 1960, and in 1970, 21 separate Year Books were published.

Very few readers are aware of the tremendous amount of thought and work that goes into the making of the Year Books. Each year over 50,000 articles taken from thousands of individual journals are classified by hand and sent to the 52 medical editors for evaluation. The medical editors select a predetermined number of outstanding articles and return them to the publisher for abstracting and preliminary editing. The abstracts are returned to the medical editors for critical review. At this time, the medical editors add their editorial comments that help the reader to place the individual abstracts in perspective. The abstracts are then arranged in manuscript order by the medical editors and returned to the publisher to be placed in production. The 21 Year Books each year contain over 7,000 abstracted ar-

ticles, nearly 3,000 illustrations and more than 5,000 editorial comments.

It is of interest to add that Year Book Medical Publishers has experienced an even greater expansion in the publication of medical monographs and textbooks than in YEAR BOOKS during the past 75 years. Today, there are over 200 active titles available to meet the information needs of the busy clinician and the medical student. We are proud to have had the opportunity to reflect the advancements in medicine for the past 75 years.

Introduction

During the 19th century, dermatology in the United States lagged far behind its European counterpart in prestige and accomplishment despite the efforts of a small number of outstanding American practitioners. Early in the 20th century, the evolution of American dermatology entered a stage of gradual acceleration that has continued to the present. The YEAR BOOK of DERMATOLOGY was founded in 1902, a most propitious time. It is a tribute to the past editors that browsing through the previous issues of the YEAR BOOK rewards the reader with a clear picture of the constantly changing patterns of emphasis in clinical and investigative dermatology.

From 1902 to 1914, dermatology was included in the YEAR BOOK OF NERVOUS AND MENTAL DISEASES, which to some might still seem an appropriate association. The Skin and Venereal Disease section was edited by William L. Baum of Chicago. The introductory chapter of the 1902 issue dealt with constitutional relationships of skin diseases and included stimulating discussions of "contagious" (Ritter's disease) and "childhood" pemphigus (toxic epidermal necrolysis) and congenital ichthyosiform erythroderma, in which the bullous and dry forms of the disease were recognized as distinct entities.

In 1907 the YEAR BOOK reflected on and contributed to the controversy over the pathogenic significance of Schaundinn's *Treponema pallidum*. The flavor of the controversy is indicated by the following editorial statement: "The omnisiciently infallible attitude adopted by Schaundinn scarcely helps to clear up the matter. He claims a special instinct in detection of the pale spirochete. Such a claim is charlatanish and has long been denounced by scientists." In the same issue, there is a review of Maisonneuve's heroic study in which he inoculated himself with virulent spirochetes injected into the sulcus coronarius in order to prove the effectiveness of his calomel-lanolin prophylactic regimen.

By 1915, when Ormsby and Mitchell assumed the editorial duties, the *T pallidum* controversy was long settled, but syphilologists were busily engaged in devising more effective arsenical treatment regimens. The reader of that volume received a bonus in the miscellaneous section with the provocative contribution of L. A. Stone on feminism. "He does not believe that woman will ever possess the true spirit of democracy, that she is too fond of pomp and show; . . . . she becomes filled with the autocratic spirit sooner or later because of the influence and money showered on her." During the 1920s diagnosis and treatment of syphilis and general clinical dermatology continued to dominate the YEAR BOOK.

Wise and Sulzberger assumed the editorship in 1931, a crucial period in the development of American dermatology. The American Board of Dermatology was in the process of organization. Its establishment in 1932 set standards of proficiency that gained respect for the field of dermatology and provided a foundation for further expansion. The YEAR BOOK of Dermatology reflected those changes, and indeed may have contributed to them by providing a concise source of information concerning progress in the field. During the 1930s, practical clinical articles remained the principal content of the YEAR BOOK, but the editors recognized the growing influence of investigative studies, especially in allergy and immunology. Investigative studies were, of course, somewhat limited in scope and simplistic in methodology, though the ingenuity of investigators resulted in steady progress.

The 1940s and World War II were exciting, revolutionary years for dermatology. Dermatologic conditions were responsible for much morbidity in military personnel, and syphilis was "conquered" along with many other infectious cutaneous diseases. The emergence of radiobiology and nuclear medicine made inroads on the therapeutic use of x-rays in dermatology, and dermatologic investigators began applying more sophisticated laboratory technics to their work. The 1950s brought the adrenal steroids, which allowed the dermatologist to control some of the most serious diseases seen in his practice. Locally applied steroids induced a slow death to the art of individually compounded dermatologic medications, leading to the rapid development of dermatologically oriented pharmaceutical companies. Perhaps the most outstanding dermatologic event during the 1950s was the publication of Stephen Rothman's *Physiology and Biochemistry of the Skin* (Chicago: University of Chicago Press, 1954). That volume, a comprehensive compendium of data subjected to provocative critical analysis, was a reference source and inspiration for a proliferating group of investigators who assembled at established and newly organized university dermatology departments. The emergence and expansion of basic and applied laboratory research was the outstanding accomplishment of dermatology in the 1960s. This trend has continued somewhat diminished into the 1970s. The YEAR BOOK OF DERMATOLOGY has monitored these events as faithfully as the proclivities of the editors has allowed.

FREDERICK D. MALKINSON
ROGER W. PEARSON

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THE PORPHYRIAS: BASIC SCIENCE ASPECTS, CLINICAL DIAGNOSIS AND MANAGEMENT*

LEONARD C. HARBER, M.D.,† AND DAVID R. BICKERS, M.D.‡

†*Professor and Chairman, Department of Dermatology, College of Physicians and Surgeons, Columbia University*

‡*Assistant Professor, Department of Dermatology, College of Physicians and Surgeons, Columbia University, and Career Scientist of the Health Research Council of the City of New York*

INTRODUCTION

Current understanding of porphyrin metabolism can be dated from 1925, when Hans Fischer isolated crystalline materials from the urine of a patient with marked photosensitivity and named these substances "uroporphyrin" and "coproporphyrin."[1] Probably the first clinically reported case of cutaneous porphyria was that described by Schultz in 1874 under the name "pemphigus leprosus."[2] The patient, who suffered from liver disease, marked photosensitivity and hemolytic anemia, was shown to excrete urine with excessive amounts of an unknown pigment. In retrospect, this may well have been uroporphyrin. During recent years, clinical and biochemical investigations of disorders of porphyrin metabolism have utilized the cooperative efforts of diverse disciplines including photochemistry, biophysics, biochemistry, hematology and dermatology. These studies have enhanced our understanding of both the chemistry of heme synthesis and the clinical diseases known as the porphyrias, which are associated with abnormalities in this biochemical pathway.

The purpose of this review is to integrate newer knowledge of porphyrin metabolism with the photosensitivity seen in the cutaneous porphyrias, at the same time stressing those aspects that are particularly pertinent to the diagnosis and treatment of these diseases in dermatologic practice.

The porphyrins exist in nature as components of three broad groups of compounds: heme, chlorophyll and cobalamin, each of which is fundamentally a cyclic tetrapyrrole. Although there are minor structural differences among them, each is characterized by the metal with which it chelates. Heme contains iron, chlorophyll contains magnesium and cobalamin contains cobalt.

Heme, primarily known for its role in transporting oxygen as hemo-

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TABLE 1.—CLASSIFICATION OF PORPHYRIAS*

- Erythropoietic
  - Erythropoietic porphyria (R)
  - Erythropoietic protoporphyria (D)
  - Erythropoietic coproporphyria (D)
- Hepatic
  - Porphyria cutanea tarda
    - Alcohol, hormone or drug induced
    - Tumor or infection
    - Hereditary (D)
  - Acute intermittent porphyria (D)
  - Porphyria variegata (D)
  - Hereditary coproporphyria (D)

*R, recessive trait; D, dominant trait.

globin, is the prosthetic group for numerous enzymes, including catalases, peroxidases and cytochromes.

Chlorophyll serves as a superb "solar energy trap" which is essential to life. Plants containing this magnesium-chelated tetrapyrrole absorb solar energy and through a series of enzymatic reactions convert carbon dioxide in the presence of water into oxygen and sugar. Thus, absorbed solar energy or radiation is transformed into chemical energy and stored in the form of carbohydrates. This fundamental process, commonly known as photosynthesis, represents an enzymatically controlled photosensitivity reaction that is beneficial to living organisms, as compared with other types of uncontrolled photosensitivity reactions that may be injurious or lethal.

The third group of porphyrins, the cobalamins, are necessary for maturation of normal erythrocytes. Pernicious anemia, with its associated peripheral neuropathy, results from decreased absorption of this tetrapyrrole.

It is thus clear that porphyrins are critical for numerous fundamental metabolic activities required for normal function. Indeed, neither uroporphyrinogen and coproporphyrinogen, the normal intermediates of the heme pathway, nor their oxidized counterparts, uroporphyrin and coproporphyrin, are themselves toxic, but when present in excess may be associated with disease. The porphyrins can accumulate in concentrations several hundred- to several thousand-fold above normal levels in selected patients.

Studies by Watson *et al*[3] and Schmid *et al*[4] first clearly postulated that disorders in heme synthesis may involve the bone marrow or liver or both tissues. Table 1, which will serve as a framework for subsequent discussion, represents a general classification of the porphyrias, emphasizing their pattern of inheritance and the major site of production of excessive porphyrins in these diseases.

BIOCHEMISTRY OF PORPHYRIN—HEME SYNTHESIS

Of all the biochemical pathways known in living cells, heme synthesis is one of the better defined in terms of its chemical components

as they relate to structure and function. Because of their unique ability to bind and release oxygen, the hemes of various proteins play a central role in many energy-producing reactions of intermediary metabolism. A well-known example of this phenomenon is illustrated by hemoglobin, a heme protein which is found in the erythrocyte and functions in the transport of oxygen from the environment (inspired air) to the tissues. Another example of the role of heme as an "oxygenator" is that of cytochrome P-450, another heme protein. This moiety, which is localized primarily in the endoplasmic reticulum of liver cells, functions as an "oxidase" and is able to metabolize a wide variety of drugs, exogenous chemicals and endogenous steroid hormones. The metabolic activity of cytochrome P-450 is critical for the biotransformation of chemical substrates into biologically inactive and more highly water-soluble substances, which can then be more readily excreted by the kidney. These two functions of heme are cited simply to demonstrate the importance and the ubiquitous distribution of this moiety in fundamental biochemical processes.

The heme biosynthetic pathway begins in the mitochondrion of the cell, where two precursors, succinate and glycine, are found in abundance (Fig 1). Classic studies by Shemin and co-workers showed that isotope-labeled glycine was incorporated into circulating heme of hemoglobin and that succinate, a four-carbon intermediate of the tricarboxylic acid cycle, could react with glycine to form an aminoketone, δ-aminolevulinic acid (ALA).[5-7] The enzyme δ-aminolevulinic acid synthetase (ALAS), which catalyzes this reaction, is localized in the mitochrondrial matrix and has a regulatory function for the entire heme synthetic pathway. Numerous studies have demonstrated that ALAS enzyme activity is rate limiting for heme synthesis; stated in another way, the activity of this enzyme determines the rate at which the end product (heme) is produced. When ALA is added to tissues it is rapidly converted to porphyrins, whereas added glycine and succinate are not so converted, indicating that ALAS is rate limiting for the pathway.[8] Granick and Urata demonstrated that the drug 3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC) could induce increased activity of hepatic ALAS in guinea pigs whereas the activity of all the remaining enzymes in the pathway was not altered significantly.[9] These studies indicate that ALAS activity is the primary determinant of the amount of heme that is produced in the cell. Since the other enzymes in the heme pathway are not limiting, most of the ALA formed from succinate and glycine by ALAS is subsequently converted to heme. It is this end product of the pathway, heme, that is utilized as a prosthetic group by a protein such as globin to form hemoglobin. The remarkably efficient use of the enzymatically produced ALA accounts for the fact that, under normal conditions, only trace amounts of it and other porphyrin intermediates can be detected in healthy persons. Abnormalities in this precise control of heme synthesis lead to the accumulation of excessive amounts of intermediates which are then associated with diseases classified as the porphyrias. The porphyrias, therefore, reflect biochemical abnormalities of heme

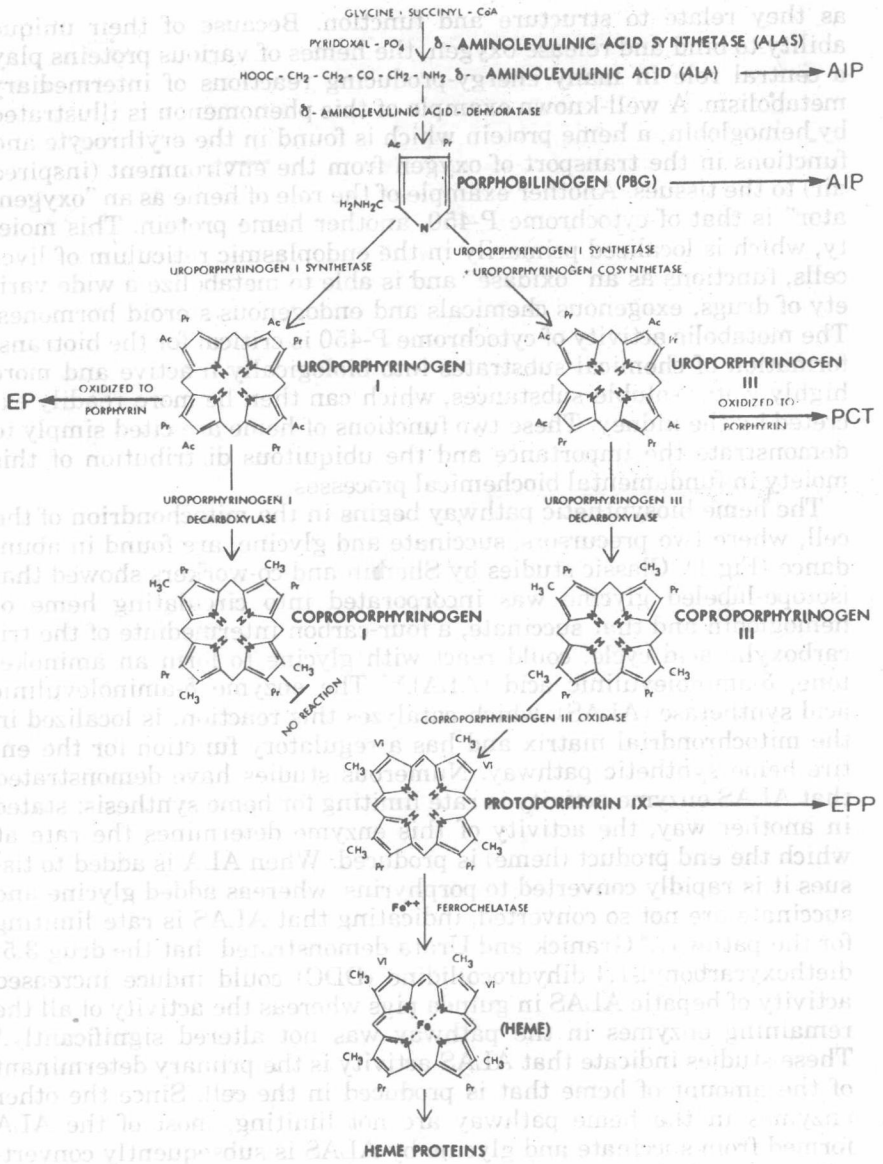

Fig 1.—Schematic outline of heme synthesis. The amino acid glycine is combined with succinyl-CoA in the presence of an enzyme, δ-aminolevulinic acid synthetase *(ALAS)*, to form δ-aminolevulinic acid *(ALA)*. Two moles of ALA condense to form porphobilinogen *(PBG)*. Type I and type III porphyrinogen isomers are rapidly synthesized. However, it is only type III isomers that eventuate in protoporphyrin and heme synthesis. Enzymatic defects caused by genetic and/or environmental factors may lead to the accumulation of heme precursors characteristic of acute intermittent porphyria *(AIP)*, porphyria cutanea tarda *(PCT)*, erythropoietic porphyria *(EP)* and erythropoietic protoporphyria *(EPP)*. *Ac*, acetyl; *Pr*, propionyl; and *Vi*, vinyl.

synthesis and manifest themselves as specific cutaneous and systemic syndromes.

The precision with which the pathway is regulated has suggested that most of the time the rate-limiting ALAS is highly repressed and that the activity of the enzyme is short-lived. It has been calculated that the half-life of mammalian hepatic ALAS is only 1–2 hours.[10] Thus, continuous production of the enzyme is required in order to maintain a continuous supply of heme.

Control of the activity of ALAS, and hence of heme production, is thought to be determined by the amount of end product (heme) that is present within the cell (Fig 2). The classic studies of Jacob and Monod[11] have shown such a control mechanism does exist in bacteria. They demonstrated that the end product of a biosynthetic pathway may function as a corepressor. When this corepressor combines with an aporepressor-protein in the cell, a complete repressor molecule is formed. This repressor is then able to block (repress) the structural gene (DNA) that codes for the synthesis of a particular protein, ie, ALAS. Although no incontrovertible evidence for this type of control has been demonstrated in mammalian systems, the concept provides an hypothesis that can explain the known responses of the heme pathway to certain drugs and chemicals (Fig 2). Using elegant

Fig 2. – Schema for repressor-operator control of ALA synthetase (ALAS) formation (Jacob and Monod model). Heme (iron-protoporphyrin), at a critical concentration, may combine with an aporepressor to form a repressor; the repressor may then exert an inhibitory effect on the operator gene. The operator regulates the activity of a structural gene that transcribes the messenger RNA for ALAS. This messenger is the template for the synthesis of ALAS, the rate-limiting enzyme for heme synthesis. Inducer chemicals (drugs and hormones) may lead to increased ALAS activity by interfering with the role of heme as a corepressor which can lead to derepression of the operator gene.